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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/564,932	THEOBALD ET AL.	
	Examiner	Art Unit	
	SAVITHA RAO	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-12 and 14-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-12 and 14-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-3, 6-12, 14-18 and 19-20 are pending.

Receipt and consideration of Applicants' amended claim set and remarks/arguments filed on 03/02/2010 is acknowledged. Claims1 and 18 are amended and new claims 19-20 are added.

Applicants' arguments, filed 03/02/2010, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112

(New matter rejection)

This rejection is necessitated by the newly submitted claims filed on 10/17/2008

> The following is a quotation of the first paragraph of 35 U.S.C. 112:
> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 and dependent claims 2-3, 6-12, 14-17 and 19-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 1 recites "the polymer layer is disposed **directly** on the backing layer" in the first line of the claim.

For the amendment to instant claim 1 which included the term "directly" applicants state that the support can be found in their application as filed on page 12, lines 15-25. However, it is noted that the lines cited by the applicant recite as follows:

> Example 2
> A TTS consisting of backing layer and two active ingredient-containing layers is produced. The first active ingredient-containing layer (reservoir layer) consists of 40 % by weight of pramipexol (base) and 60 % by weight of Durotak 2287 and has a basis weight of 100 g/m^2. The second active ingredient-containing layer (pressure-sensitive adhesive layer) consists of 3 % by weight of pramipexol (base) and 97 % by weight of Durotak 2287 and has a basis weight of 30 g/m^2. TTS samples for the in vitro investigations are cut out of

The above recitation is just stating that a TTS consisting of a backing layer and two active ingredient-containing layers is produced. Nowhere in the recitation does it state that "**the polymer layer is disposed directly on the backing layer".** Other sections of the instant disclosure also fail to lend support to this limitation. As such introduction of the term "directly" in instant claim 1 constitute new matter.

Consequently, there is nothing within the instant specification which would lead the artisan in the field to believe that the Applicant was in possession of the invention as it is now claimed. See *Vas-Cath Inc. v. Mahurkar*, 19 USPQ 2d 111, CAFC 1991, see also *In re Winkhaus*, 188 USPQ 129, CCPA 1975. Accordingly, claims 6 and 7 are

properly rejected under 35 U.S.C. 112 for new matter addition in the claims.

Accordingly, claims 1 and dependent claims 2-3, 6-12, 14-17 and 19-20 are properly rejected under 35 U.S.C. 112 for new matter addition in the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Rejection of claims 1-3, 6-12 14-16 and 17-20 under 35 U.S.C. 103(a) as being unpatentable over Beier et al. (WO 03/015779 as translated by US 2004/0247656,) in view of Durif et al (US 5939094) and Hoffman et al (US 4769028) further in view of Zierenberg et al, (US 5112842, already of record) and Patel et al (WO 96/39136) is maintained for reasons of record restated below.

Amendment to instant claim 1 adds the new limitation that the polymer layer is disposed directly on the backing layer. In the following rejection, Hoffmann teaches a transdermal patch comprising a protective impermeable backing layer followed by a reservoir layer (col.2, lines 4-21 and 47-68, col. 3, lines 4-6, claim1) where in the reservoir layer comprises a polymer matrix with a carrier agent or a therapeutic agent (col.3, lines 47-66). Absence of evidence to the contrary, the reservoir polymer layer of Hoffman's transdermal patch is disposed directly on the backing layer.

New claims 19 and 20 essentially recite the limitations which have already been addressed in the previously submitted claims 1-3, 6-12 and 14-18.

For e.g.: New claim 19 recites as follows:

19. (New) The transdermal therapeutic system as claimed in Claim 1, wherein the first and second active ingredient-containing polymer layers comprise pressure-sensitive adhesive polymer consisting of carboxyl group-free polyacrylates that do not comprise water or an aqueous dispersion, and the transdermal therapeutic system releases the active ingredient pramipexol with a flux rate greater than 5 µg/cm2 hr over the period between 24 hours after administration to 72 hours after administration in the absence of a penetration-promoter, and said system has no additional pressure sensitive adhesive top plaster for fixing to the skin.

20. (New) The transdermal therapeutic system as claimed in claim 19, wherein the first and second active ingredient-containing polymer layers consist of pramipexol and carboxyl group free polyacrylates pressure-sensitive adhesive.

With reference to New claim 19, previously presented claim 16, recited pressure sensitive adhesive polymer which do not comprise water or aqueous dispersion, currently amended claim 1 and previously presented claim 12 had the limitation of the release rate of the active ingredient pramipexol being at a flux rate of greater than 5 µg/cm2 over a period between 24 hours after administration to 72 hours after administration and currently amended claim 18, had the limitation that the system has no additional pressure sensitive adhesive top plaster for fixing to the skin.

With reference to new claim 20 limitations, these limitations are addressed in the following rejection as the limitations were recited in the previously presented claims 1 and 12.

With regards to the limitations in the new claim 19 "in the absence of a penetration-promoter, Beier et al. teaches a transdermal therapeutic system for the administration of pramipexol comprising an (i) an active ingredient-impermeable cover layer (ii) a plurality of active ingredient containing matrix layer (iii) a peel-off protective layer (claim 1) which does not include a penetration enhancer. In addition Beier et al. teaches that the matrix patch of his invention to consists of an impermeable cover layer, one or more self-adhesive matrix layer and where applicable a permeation enhancer/solubilizer. Clearly, Beier et al's inventive transdermal system encompasses version without the permeation enhancers. .

With regards to the limitation in the new claim 19, of no additional pressure-sensitive adhesive top plaster for fixing to the skin, Beier et al.'s inventive matrix patch does not comprise of an additional pressure sensitive adhesive top plaster for fixing to the skin as detailed below. , Durif et al. recited in the rejection below also teaches transdermal dosage forms comprising multilayered discoid patch which comprises an occlusive backing layer attached to the adhesive matrix in which a permeation enhancer and Apo morphine are dispensed in varying concentrations. Durif does not teach the presence of a pressure sensitive adhesive top plaster for fixing to the skin in his formulation. Accordingly, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to develop a transdermal therapeutic system comprising pramipexol with in a two active –ingredient containing polymer layer comprising different concentrations of active ingredient and a pressure sensitive adhesive polymer in the absence of a permeation enhancer and with no additional pressure sensitive adhesive top plaster for fixing to the skin.

Original rejection:

Beier et. al teaches an active-ingredient containing matrix-controlled transdermal therapeutic system (TTS) for the use of pramipexole, ropinirole, pharmaceutically acceptable salts thereof or pharmaceutically acceptable derivative thereof (abstract). **Beier et al. teaches a transdermal therapeutic system for the administration of pramipexole comprising an (i) an active ingredient-impermeable cover layer (ii) a plurality of active ingredient containing matrix layer (iii) a peel-off protective layer.** Beier teaches that a matrix-TTS comprising pramipexole and ropinirole as active

ingredient is to a large extent stable towards decomposition if a self adhesive matrix based on polyacrylates, especially solvent-containing polyacrylates or an polyisobutylene is used [0015]. A matrix-TTS according to **Beier consists of an impermeable cover layer, one or more self-adhesive matrix layer(s) containing the active-ingredient and where applicable permeation enhancers/solubilizer**, or one or more matrix layer(s) that are coated with a pressure-sensitive adhesive, and a peel off protective layer and the active ingredient contained in the matrix is pramipexole, ropinirole its salts or derivatives [0016]. The amount of pramipexole, ropinirole, salts or derivatives used in the transdermal therapeutic system of Beier ranges from 2-15% by weight of the matrix [0018].Beier teaches that active ingredient to be pramipexole, ropinirole or pharmaceutically acceptable salts of pramipexole or derivatives, solvates with the active ingredients such as hydrates and alchoholates [0017] Beier teaches that for pressure-sensitive adhesive layer, a pressure-sensitive adhesive based polymer such as polyurethane, polyisobutylene, polyvinylether, silicone, polyacrylate or a mixture thereof can be selected [0020] For the matrix, matrix formers customary in medicine are used e.g. polyacrylates and polyisobutylene and the matrix formers based on polyacrylates may be any desired homopolymers, copolymer or tetrapolymer consisting of various acrylic acid derivative, where applicable with vinyl acetate [0021-0022]. Beier teaches various monomers to be used in his invention which includes esters of acrylic and methacyrlic acids such as butyl acrylate, butyl methacrylate, hexyl acrylate, hexyl methacrylate, etc that may be polymerized individually or in admixture [0024]. In addition functional monomers that are compolymerisable with the acrylates and

methacyrlates include hydroxyethyl acrylate, hydroxypropyl acrylate can be used too[0025], Further more Beier teaches examples wherein the composition of a self-adhesive matrix transdermal therapeutic system for pramipexole includes pramipexole , Copherol and Durotak 2287 [0030] and [0048]. *Durotak 2287 is the polymer recommended by the applicant in the instant specification and used in the instant examples (page 7, line 34 to page 8. line 5 , example 1 and 2 on page 12 of instant application).*

The teachings of Brier differs form the instant application in that although Brier teaches multiple layer, he fails to teach the transdermal therapeutic system specifically including a second active ingredient containing polymer layer comprising between 2-10% pramipexole as recited in claim 1. Brier is also silent as to the Pramipexole being in the form of and S (-) enantiomer, the flux rate greater than 5 $\mu g/cm^2$ hr or a delivery rate of pramipexole of 0.5-4.5 mg/ day. These deficiencies are taught by Durif et al and Hoffman et al further in view of Zierenberg et al and Patel et al

Durif et al teaches dosage forms for the transdermal administration of apomorphine (abstract). Durif et al teaches that apomorphine is a powerful and effective agent for treatment of Parkinson's disease abnormalities (col.1, lines 45-60 and col.12, lines 58-64). Durif et al teaches an embodiment wherein the dosage form is a multilayered discoid patch in which the concentration of apomorphine and permeation enhancer in the adhesive matrix varies in adjacent layers (col.8, lines 22-25). Durif et al teaches dosage form that has a skin contact adhesive layer containing a relatively high concentration of a permeability enhancer such as BHT and a relatively low

concentration of apomorphine. Successive additional adhesive layers are placed upon the preceding layer, where each successive layer has a relatively lower concentration of permeation enhancer and a relatively higher concentration of apomorphine present and an occlusive backing layer is present as the top layer of the dosage form (col.8, lines 34-47). One embodiment of the dosage form of the present invention is a transdermal patch that contains an occlusive backing layer attached to the adhesive matrix on a face opposed to the surface capable of adhesively contacting a skin surface, and a release liner attached to the skin contact surface of the adhesive matrix. The adhesive matrix in this particular embodiment contains the pressure-sensitive medical-grade silicon adhesive, a permeation enhancer and apomorphine and may can contain a plurality of layers where each successive layer contains in addition to the adhesive varying concentrations of apomorphine and/or a permeation enhancer (col.12,lines 35-51). As such Durif et al provides an ordinarily skilled artisan ample motivation to develop a transdermal therapeutic system comprising two different layers, each containing the adhesive matrix with varying concentration of active ingredient.

Hoffmann teaches a transdermal patch for drug delivery of such therapeutic agents as antimigraine agents, comprising a protective impermeable backing layer, a reservoir layer, an adhesive layer, and a removable cover layer (column 2, lines 4-21 and 47-68; column 3, lines 4-6; claim 1). The backing layer is the outermost layer of the patch, the reservoir layer is adjacent to, and in contact with, the backing layer and contains the drug or drugs at a high concentration (supersaturated), the adhesive layer is positioned immediately after the reservoir layer and can contain the active agent in a concentration

lower than in the reservoir layer, and the removable covering is attached to the adhesive layer (column 2, lines 48-68; column 3, lines 1-6; Figure 1). The reservoir layer further comprises a polymer matrix, such as polyisobutylene and other polymers which have been used in the production of pressure sensitive adhesive materials may be used, and can also comprise carrier agents for the therapeutic agent, and/or a filler (column 3, lines 47-66; column 4, lines 1-6; Example 1). Hoffmann additionally teaches that the transdermal therapeutic system of his invention can be used to other therapeutically active agents which are administered to the skin (col.4, lines 17-23). The adhesion layer further comprises a polymer matrix, such as polyisobutylene, and can also comprise carrier agents for the therapeutic agent, and/or a filler (column 4, lines 38-51; column 3, lines 47-66; column 4, lines 1-6; Example 1). Although Hoffmann does not teach specific amounts of the components of the compositions, Hoffmann does teach that the desired release rate of the active agent can be controlled by adjusting the composition of the polymer matrices, the concentration of the active agent in the reservoir and adhesive layers, the concentration gradient, and the kind and amount of carrier agents (column 5, lines 13-32). Hoffmann also teaches some embodiments in which the reservoir layer is made up of multiple layers with different concentrations of active agent (concentration increases as distance from skin increases, or as the layers get closer to the backing layer). Hoffman further teaches that the various individual layers of the reservoir layer may be produced from either the same or different polymer matrix and the therapeutically desired amount is determined by the kind of the active agent or agents, the intended time of the application of the medical

bandage and the intended therapeutic field or therapeutically indication for the pharmaceutical product. Hoffman et al additionally teaches that the ratio of drug concentration in g per cm3 in the individual layer of the supersaturated reservoir layer adjacent to the adhesive layer to the drug concentration in the individual layer of the supersaturated reservoir layer closest to the cover layer is within the range of 1:1.1 to 1:20, preferably 1:2 to 1:20.

Neither Durif et al nor Hoffman et al teaches the instantly Pramipexole being in the form of and S (-) enantiomer, finally the flux rate greater than 5 $\mu g/cm^2$ hr or a delivery rate of pramipexole of 0.5-4.5 mg/ day.

However, Zierenberg et al teaches transdermal administration of 2-amino-6-n-propylamino-4,5,6,7-tetrahydrobenzothiazole (Pramipexole) or the (-) enantiomer thereof and transdermal systems containing these active substances (abstract). Zierenberg teaches that transdermal administration of Pramipexole, doses of 2 mg per day can be administered without an orthostatic side effects occurring in the patient, which corresponds to 10 times the amount which can usually be administered by oral application of the substance (col.1, lines 30-38). Zierenberg additionally teaches that although the solution to his invention is not limited to the use of a specific transdermal therapeutic system, provided the system ensures an adequate release of active substance-systems which have an active substance reservoir consisting of an emulsion polymerized polyacrylate are preferred according to his invention. Using such systems Zierenberg teaches that it is possible to administer 2-amino-6-n-propylamino-4,5,6,7-tetrahydrobenzothaizole or the (-) enantiomer thereof in a dose of 0.5-5 mg per day

without any orthostatic side effects being observed (col.1, line 49 to col.2, line10, claim 9). Zierenberg additionally teaches that his system consists of a backing layer which is impervious to the active substance and is simultaneously as a covering plaster to secure the system to the skin, a reservoir containing the active substance and a removable protective film which protects the system before it is ready to be used and the preferred carrier material polyacrylate is the type marketed as Eudragit NE (a mixture of carboxyl-group-free polymerized acrylic esters and methacrylic esters). The proportion of the active substance in the reservoir is between 5-30% preferably between 7-15% by weight (col.2, line 11-23).

Patel et al. teaches transdermal formulations comprising ropinirole for use in treating Parkinson's disease (abstract). Patel teaches that the transdermal formulation offers the advantage of a more convenient mode of administration of the drug substance, thereby potentially enhancing patient compliance and in addition, drug substance is released in a more controlled fashion, over a prolonged period, offering potential therapeutic advantages (page 1, lines 29-32). Patel teaches that the transdermal system of his invention will provide a steady rate delivery, or alternatively a compartmentalized rate controlled system and a suitable target skin flux will be in the range of 5-25 preferably in the range of 10-15 ug/cm^2/hr (page 3, lines 10-13 and page 7, claims 2). Patel teaches the transdermal formulation to be provided in a unit dose form, in a range of dosage amounts, for instance to allow for titration of an individual patient's drug requirement and a suitable dose may be obtained by combining different strength formulation. Patel teaches a unit dose form to provide sufficient drug substance

for a 24 hour period to permit once-a-day application of the formula (page 3, lines 21-28). Patel also teaches the penetration of drug from the transdermal system of his invention over 254 hours and 96 hours in Example 3 (page 5-6) where in ropinirole free base displays a penetration of about 10-20 ug/cm^2 over 24 hours and 30-84 ug/cm^2 of the drug had penetrated over a period of 96 hours. Both Pramipexole and Ropinirole are non-ergoline dopamine agonists commonly used in the treatment of Parkinson's disease as evidenced by D.J Brooks (J. Neurol.Neurosurg. Psychiatry, 2000; 68; 685-689) who teaches on page 687, under the heading Non-ergoline Agonists that ropinirole and pramipexole are both new dopamine both of which act as agonists of D2-type receptors. Therefore, Pramipexole and Ropinirole are functional equivalents. Additionally, Beier et al, teaches the use of these two drugs together in a transdermal system providing a suggestion that one of ordinary skill in the art could use pramipexole in place of Ropinirole in the transdermal system taught by Patel.

With regards to the limitation in instant claims 1, 14 and 18 of the concentration by weight of the pramipexole in the first and the second active-ingredient layer, Beier teaches his transdermal therapeutic system to comprise pramipexole or ropinirole at a concentration of 2-15% by weight of the matrix. Beier as such provides an ordinary skilled artisan a starting concentration to optimize the active ingredient. Additionally, Hoffmann teach that the desired release rate of the active agent can be controlled by adjusting the composition of the polymer matrices, the concentration of the active agent in the reservoir and adhesive layers, the concentration gradient, and the kind and amount of carrier agents. Hoffman additionally teaches the ratio of the active ingredients

in subsequent matrix layers which provides an ordinarily skilled artisan teaching as to optimize the concentration of the active ingredient among the different layers. As such determination of the amount of active ingredient which needs to be incorporated in the various matrix layers in a multi layer transdermal therapeutic system would have been obvious to one of ordinary skill in the art at the time of this invention. Additionally, It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

In view of the foregoing references it would have been *prima facia* obvious for one of ordinary skills to develop a therapeutic transdermal system as instantly claimed with two layers comprising active ingredient at different concentrations. Because Beier teaches that a matrix-Transdermal Therapeutic System comprising pramipexole and ropinirole as active ingredient is to a large extent stable towards decomposition if a self adhesive matrix based on polyacrylates is used, Durif et al and Hoffman et al teaches transdermal systems with more than one pressure sensitive adhesive layer comprising different concentrations of the active ingredient, Zierenberg teaches the reduction of orthostatic side effects in delivering pramipexole as transdermal therapeutic form and Patel teaches that transdermal forms offers several advantages over oral administration such as patient compliance and controlled delivery of the drug. Accordingly, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to develop a transdermal therapeutic system comprising pramipexole with in a two active – ingredient containing polymer layer comprising different concentrations of active

ingredient and a pressure sensitive adhesive polymer. An ordinarily skilled artisan will be imbued with at least a reasonable expectation of success based on the state of the art at the time of invention that such a transdermal therapeutic system would be an effective system for delivery of pramipexole as it offers longer duration of constant delivery and higher stability.

With regards to limitations claimed in instant claim 11 wherein the drug is delivered continuously to a patients' skin over a period from 4 to 7 days, and limitations in the instant claims 1 and 12 of the active ingredient being released over a period between 24 hours after administration to 72 hours or 168 hours, designing transdermal therapeutic systems for delivery of drugs continuously for desired time period at the rate is well known in the art as evidenced by Scheindlin (Molecular Interventions 4: 308-312 (2004)) who teaches on page 308, the scopalamine patch is worn behind the ear and releases the alkaloid for three days, preventing motion sickness without the need to swallow tablets periodically, the fentanyl patch acts for seventy-two hours, providing long lasting pain relief and an estrogen-progestin contraceptive patch which has to applied once a week. Accordingly, one of ordinary skill in the art would be able to formulate the transdermal therapeutic system for pramipexole as taught by Beier, Zierenberg and Patel to have the desired release profile ranging from once a day to once a week administration.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Claims under 35 U.S.C. 103(a) as being unpatentable over Beier et al. (WO 03/015779 as

translated by US 2004/0247656) in view of Durif et al, Zierenberg et al, (US 5112842) and Patel et al (WO 96/39136) as applied to claims 1-3, 6-12 14-15 and 17-18 above further in view of Wick et al (US 5238944, already of record)

Teachings of Beier, Durif et al, Hoffmann et al, Zierenberg and Patel are as discussed supra and are applied here in the same manner.

Durif et al additionally teaches his inventive transdermal system to comprising a pressure-sensitive medical grade silicone adhesive mixture which contains apomorphine and a penetration enhancer (col.3, lines 39-44, and col.9, lines 31-41). Durif et al additionally teaches the method of preparation of the silicone pressure sensitive composition which does not comprise water or an aqueous dispersion (col.9, lines 42-col.11, line 66).

The cited references do not teach the pressure sensitive adhesive monomer mixture comprising vinyl acetate in a proportion of between than 25% by weight.

Wick et al. teaches pharmaceutical formulations and adhesive-coated sheet materials for transdermal delivery (abstract). In one of the embodiment of the pressure sensitive adhesive composition, Wick et al teaches the adhesive copolymer to comprise about 60-80% by weight of the hydrophobic monomeric acrylic or methacyrlic acid ester of an alkyl alcohol, 4-9% of reinforcing monomer selected from the group consisting of acrylic acid, methacrylic acid etc. and about 15-35% by weight of vinyl acetate based on the total weight of all monomer in the copolymer.

As such, use of pressure sensitive adhesives as taught by the above references was well known in the pharmaceutical art at the time of the invention. Pressure

sensitive adhesive compositions comprising co-polymers of monomeric acrylic or methacrylic acid with vinyl acetate was also known in the art at the time of the invention. Accordingly, it would have been obvious to one skilled in the pharmaceutical art to optimize the known polymers suitable for preparing pressure sensitive adhesives and its concentration to arrive at a composition of pressure sensitive adhesive layer which would provide good adhesion to the skin and optimal delivery of the drug through the skin. As such an ordinarily skilled artisan would apply the knowledge of developing an appropriate pressure sensitive adhesive as taught by Durif and Wick to be used in the pramipexole transdermal delivery system taught by Beier, Durif, Hoffman Zierenberg and Patel with a reasonable expectation of success.

Response to Applicant's argument submitted on 03/02/2010

Applicant's traverse the above rejection with the following arguments:

1. The primary reference Beier et al (US 733) teaches moderate amounts of pramipexol within a single layered matrix that further includes a penetration enhancer.

2. The newly cited references are not directed to pramipexol; US 094 (Durif et al.) merely incorporates apomorphine in amounts of to 10 % into a silicone adhesive that further contains a penetration-enhancer. US 028 (Hoffman et al.) incorporates any of a laundry list of active ingredients into silicon rubber or the like in undisclosed amounts., however, expressly teach that elevated quantities of active ingredients within an adhesive layer require an additional adhesive intermediary layer between the adhesive layer and the backing layer. US 842 (Zierneberg et al.) merely teaches single layered pramipexol TTSs formed from water-based polyacrylate that further include a covering

plaster. WO 136 (Patel et al.) merely discloses ropinirole in undisclosed amounts within a water-based matrix sufficient for once-a-day application.

3. The cited references, considered either alone or in combination, simply do not teach or suggest the inventive multi-layered TTSs containing an active ingredient layer formed from carboxyl-group-free polyac13date pressure-sensitive adhesive polymer that contains up to 75 % pramipexol disposed directly on a backing layer, much less such a TTS providing a flux rate greater than 5 gg/cm2 hr up to 72 hours after administration. And the combination most certainly does not teach or suggest such TTS that do not include penetration enhancer or a covering plaster.

Applicant's arguments presented above while considered by the examiner, is not found to be persuasive.

First, it should be noted that the above rejection was made under 35 U.S.C. 103(a) and therefore none of the cited references has to teach every limitation of the instant claims. Applicant is further reminded that the obviousness rejection is not an anticipation rejection. The combination of the above mentioned references clearly teach a multi layered transdermal therapeutic device, comprising pramipexol with in two active ingredient containing polymer layers wherein the polymer is pressure sensitive adhesive polymer. In obviousness rejection a combination of references is used, and the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references that make up the state of the art with regard to the claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art

represented by the combination of the cited references. *In re Young*, 403 F.2d 754, 159 USPQ 725(CCPA 1968); *In re Keller 642 F.2d 413, 208 USPQ 871 (CCPA 1981).*

Moreover, it is noted that rejections under 35 U.S.C. 103(a) are based on combinations of references, where the secondary references are cited to reconcile the deficiencies of the primary reference with the knowledge generally available to one ordinary skill in the art to show that the differences between Applicant's invention and the prior art are such that they would have been modifications that were *prima facie* obvious to the skilled artisan. It is noted that the claimed invention is not required to be expressly suggested in its entirety by any one or all of the references cited under 35 U.S.C. 103(a). Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

In response to applicant's arguments against each references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). For example. In the instant case, (i) although Beier dose not specifically teach the pramipexole being in the S (-) enantiomer form, Zierenberg teaches this limitation. (ii) Although Beier does not teach the flux rate of the active ingredient release, this limitation is taught by Patel et al. (iii) Although Beier only teaches a moderate amount of pramipexol in their system as alleged by the applicant, Hoffman teaches that the desired release rate of the active agent can be controlled with the concentration of the

active ingredients in the subsequent matrix layers which provides an ordinarily skilled artisan motivation to optimize the amount of active ingredient which needs to be incorporated in the various matrix layers in a multi layer transdermal system. (iv) **Beier et al. while suggesting a plurality of active ingredient containing matrix layer** is further supported by the teachings of Durif et al and Hoffman et al who teaches more of such systems and further provides an ordinarily skilled artisan suggestions as to the method of preparing such systems and their advantages. As such In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). All the references here are drawn towards the same art which is transdermal delivery of therapeutic substances. Accordingly, an ordinarily skilled artisan in the pharmaceutical arts at the time of the invention would be motivated to combine the teachings of these references to arrive at the instant invention.

In response to applicants argument that combination most certainly does not teach or suggest such TTS that do not include penetration enhancer or a covering plaster. Applicants are referred to the teachings of , Beier et al. Beier et al. teaches a transdermal therapeutic system for the administration of pramipexol comprising an (i) an

active ingredient-impermeable cover layer (ii) a plurality of active ingredient containing matrix layer (iii) a peel-off protective layer (claim 1) which does not include a penetration enhancer. In addition Beier et al. teaches that the matrix patch of his invention to consists of an impermeable cover layer, one or more self-adhesive matrix layer and where applicable a permeation enhancer/solubilizer. Clearly, Beier et al's inventive transdermal system encompasses version without the permeation enhancers (See reference claim 1 vs. reference claim 8). In addition, Beier et al.'s inventive matrix patch does not comprise of an additional pressure sensitive adhesive top plaster for fixing to the skin as detailed below. , Durif et al. recited in the rejection above also teaches transdermal dosage forms comprising multilayered discoid patch which comprises an occlusive backing layer attached to the adhesive matrix in which a permeation enhancer and Apomorphine are dispensed in varying concentrations. Durif does not teach the presence of a pressure sensitive adhesive top plaster for fixing to the skin in his formulation. Accordingly, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to develop a transdermal therapeutic system comprising pramipexol with in a two active –ingredient containing polymer layer comprising different concentrations of active ingredient and a pressure sensitive adhesive polymer in the absence of a permeation enhancer and with no additional pressure sensitive adhesive top plaster for fixing to the skin.

As such, Applicants arguments do not overcome the instant rejection and further, the applicants have not presented any unexpected results or secondary considerations to overcome the rejection. The rejection is therefore maintained.

Conclusion

Claims 1-3, 6-12 14-16 and 17-20 are rejected. No claims are allowed

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7.00 am to 4.00 pm..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAVITHA RAO/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614